

## Onco-Nephrology: Core Curriculum 2015

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The overlap between oncology and nephrology is an area of growing importance. A major reason for this is that less than half the patients with cancer were long-term survivors years ago, whereas now more than two-thirds will live 5 years or longer. Late effects of cancer treatment include nephrotoxicity and are part of current clinical practice. In addition, cancer is now a known feature of chronic kidney disease (CKD), with increased risk in patients receiving dialysis or with a functioning kidney transplant, as well as those with earlier stages of the disease. Therefore, oncologists will refer patients to nephrologists, and nephrologists will need to consult oncologists. This Core Curriculum addresses the key issues at this challenging clinical interface.

## ASSESSMENT OF KIDNEY FUNCTION

## Clinical Practice

Kidney function determines the choice of cancer treatment, and its decline is a serious adverse event for patients with cancer. The number of nephrons corresponds closely to the total glomerular filtration rate (GFR) of a given patient. Thus, the practical concept of kidney function is usually the same as that of the GFR. The gold-standard measurement of GFR is by inulin or iothalamate clearance, but those are rarely done in clinical practice. A 24-hour urine collection enables measurement of urea and creatinine clearances, which can be averaged to estimate GFR. Formulas can correlate serum creatinine level to iothalamate clearance. The best known estimation formulas are the MDRD (Modification of Diet in Renal Disease) Study equation and the CKD-EPI (CKD Epidemiology Collaboration) equation. The formula-derived value for GFR is commonly reported by clinical chemistry laboratories. This value is not 100% accurate or precise because of measurement and biological variability. The formula-derived estimated GFR (eGFR) cannot be used for patients whose kidney function is rapidly changing. It also is not reliable in patients who have lost muscle mass because they have relatively lower creatinine generation. This results in lower serum creatinine levels, causing overestimation of GFR as compared to the true value. Twenty percent or more of patients with cancer may have sarcopenia, that is, significant loss of muscle mass, and thus will have lower-than-expected serum creatinine levels. This can lead to medication dosing that results in side effects and toxicities because the patient's actual GFR is

significantly lower than the eGFR reported by the laboratory. In these patients, determining the true GFR by using 24-hour urine collections (or even the more expensive iothalamate clearance) may be needed.

## Laboratory Measurement

Neither serum creatinine level nor the eGFR derived from it has pinpoint accuracy or precision. The critical value difference of serum creatinine level is 0.2 mg/dL when its absolute value is close to normal. That means that a day-to-day change < 0.2 mg/dL may just be noise and not significant. The critical value difference for serum creatinine level is higher when its absolute value is higher. Although most clinical chemistry laboratories use an enzymatic method, some may use the Jaffé method, which may give an artifactually low serum creatinine value in patients with immunoglobulin G paraproteinemias.

## Relevant Clinical Investigation

Other ways of assessing kidney function have been tested in patients with cancer. Using the cystatin C assay in the general population may slightly increase the accuracy of eGFR, but not to the extent of justifying its routine use. Seventy-five percent of active clinical cancer research studies registered on [ClinicalTrials.gov](http://ClinicalTrials.gov) exclude patients with reduced kidney function, limiting our knowledge of cancer treatments in this population. Patients with CKD and cancer have a higher mortality rate than patients who have cancer but not CKD. Although it may be possible to improve the precision and accuracy of clinical assessment of kidney function, a higher priority is to include patients with reduced kidney function in cancer trials.

## Tubular Function

Toxicity from chemotherapy may be primarily tubular. Magnesium wasting from cisplatin or epidermal

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growth factor inhibitors and Fanconi syndrome from ifosfamide are well known. Changes in renal excretion of ions can be detected by calculation of their fractional excretion from ion and serum creatinine concentrations; that is,  $\frac{[(\text{urine ion}) \times (\text{serum creatinine})]}{[(\text{urine creatinine}) \times (\text{serum ion})]} \times 100$ , taking care to use the filterable serum ion concentration and comparing the obtained value to that expected for the simultaneous GFR level.

Subtle tubular toxicity from chemo- or radiotherapy may not change the serum urea nitrogen or serum creatinine level very much, but may cause tubular injury that affects medication excretion. In such cases, there may be evidence of tubular injury, such as increased  $\beta_2$ -microglobulin or urinary ion excretion. However, current tests do not quantify abnormalities of tubular handling of medications. Prudent clinical observation will enable medication dose adjustments.

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## WATER AND ELECTROLYTE DISTURBANCES IN CANCER

### Electrolyte Imbalances

Electrolyte imbalances can be caused by cancer or its treatment. The following imbalances could be encountered, as summarized in Table 1.

### Hypercalcemia

Seen in up to in 20% to 30% of patients with advanced cancer and carrying a poor prognosis, hypercalcemia could result from bone metastasis (osteolytic hypercalcemia) or, in lymphoma, overproduction of 1,25 vitamin D<sub>3</sub>. Both these mechanisms will cause hypercalciuria with elevated fractional excretion of calcium. For reference, the expected fractional excretion of calcium is 1% to 2% in patients with eGFRs > 50 mL/min/1.73 m<sup>2</sup>. However, when hypercalcemia is caused by parathyroid hormone-related peptide (PTHrP), there is low urinary calcium excretion. Hypercalcemia causes polyuria (24-hour urine volume > 3 L) due to collecting duct insensitivity to vasopressin and acute kidney injury (AKI) due to volume depletion that itself aggravates the hypercalcemia. Polyuria may increase urinary potassium, magnesium, and phosphorus excretion.

Hypercalcemia is treated with parenteral saline, which restores sufficient intravascular volume. Treatment with loop diuretics is no longer recommended unless there is fluid overload. Intravenous bisphosphonates should be given as soon as hypercalcemia is diagnosed, at a dose adjusted for reduced kidney function. More recently, subcutaneous denosumab has been used, which reduces calcium release from bone. Cinacalcet, a calcium receptor sensitizer, could be used in patients with parathyroid cancer. In severe and intractable hypercalcemia in the setting of oliguric kidney failure, hemodialysis therapy with a dialysate calcium concentration < 2.5 mEq/L could be started.

### Hypocalcemia

Hypocalcemia is common in patients with cancer. Total serum calcium level may be low due to hypoalbuminemia; testing serum ionized calcium will confirm whether true hypocalcemia (serum ionized

Table 1. Electrolyte Disturbances in Cancer

Abnormality	Risk	Cause
Hypercalcemia	AKI	Increased GI absorption, reduced renal excretion, or increased bone lysis
Hypocalcemia	Tetany	Decreased GI absorption, increased renal excretion, TLS, bisphosphonates, or osteoblastic metastasis
Hyperphosphatemia	Precipitation	Increased GI absorption, reduced renal excretion, or redistribution
Hypophosphatemia	Weakness	Increased renal excretion
Hypernatremia	Thirst, lethargy	Water loss
Hyponatremia	Confusion	Water retention
Hyperkalemia	Arrhythmia	AKI, TLS, hypoadosteronism
Hypokalemia	Weakness	GI loss, hyperadrenalism
Hypermagnesemia	Arrhythmia	AKI
Hypomagnesemia	Cramps, hypocalcemia	GI loss, tubulointerstitial disease

Abbreviations: AKI, acute kidney injury; GI, gastrointestinal; TLS, tumor lysis syndrome.



calcium < 1 mmol/L) is present. If so, one must consider osteoblastic metastatic bone disease, use of bisphosphonates, magnesium depletion following cisplatin administration, or even tumor lysis syndrome (TLS) with hyperphosphatemia that has caused precipitation of calcium phosphate in tissues. Managing hypocalcemia depends on its severity. For tetany or seizures, urgent intravenous calcium chloride is required (eg, 10 mL of 10% calcium gluconate in 50 mL of 5% dextrose in water given over 10 minutes). In pauci-symptomatic true hypocalcemia due to osteoblastic bone metastases, oral calcium and 1,25-dihydroxyvitamin D could be a therapeutic option. At the same time, one addresses the cause by stopping bisphosphonate therapy, correcting hypomagnesemia, and/or treating hyperphosphatemia.

#### **Hypophosphatemia**

Hypophosphatemia could result from malnutrition in advanced cancer, paraneoplastic PTHrP secretion, or chemotherapy inducing renal phosphate wasting (ie, fractional excretion of phosphate > 15% when eGFR is in the normal range). Ifosfamide is a known culprit; a similar Fanconi syndrome could also occur after cisplatin or pamidronate use. The multitarget tyrosine kinase inhibitors imatinib, sunitinib, and sorafenib can generate hypophosphatemia as well through inhibition of bone remodelling and phosphaturia. Oncogenic osteomalacia related to tumoral fibroblast growth factor 23 (FGF-23) secretion causes phosphaturia leading to hypophosphatemia and can be debilitating.

Hypophosphatemia should be treated by oral phosphate supplementation (eg, potassium phosphate packets of 8 mmol each up to 4 times a day) or, for marked hypophosphatemia (phosphate < 1 mg/dL) by intravenous administration of phosphate (eg, 0.25 mmol/kg given over 6 hours and repeated as necessary).

#### **Hyperphosphatemia**

Hyperphosphatemia could be the result of cellular injury from rhabdomyolysis or TLS. Kidney failure is also a common cause. Extreme increases in serum phosphate concentrations may be associated with hypocalcemia due to calcium-phosphate tissue precipitation, particularly within the kidney, with a risk of acute obstructive nephropathy. Oral phosphate binders may be used for treatment, along with parenteral crystalloid. Dialysis will be needed for patients experiencing kidney failure.

#### **Hyponatremia**

Hyponatremia is very common in malignancy and increases morbidity and mortality. The initial step in evaluating hyponatremia is assessment of serum osmolality to distinguish pseudohyponatremia due to

hyperglycemia, hyperlipidemia, or hyperproteinemia from hypo-osmolar hyponatremia. The clinical symptoms depend on the speed and magnitude of hyponatremia and its cause. The condition can be observed in paraneoplastic syndromes due to inappropriate secretion of antidiuretic hormone. Those patients will be euvoletic on physical examination and have a urine sodium concentration and osmolality > 30 mmol/L and >100 mOsm/kg, respectively. The unregulated antidiuretic hormone production could be the direct result of cancers, especially those of the lung or brain. It can also result from drugs such as cyclophosphamide or vincristine. Volume depletion from tubular toxicity induced by chemotherapy or caused by nausea, vomiting, or diarrhea could lead to nonosmotic secretion of antidiuretic hormone. This will be associated with urine sodium excretion < 30 mmol/L and high urine osmolality. Finally, hyponatremia may occur in patients with cancer for the same reasons it does in the general population, for instance, from the use of thiazide diuretics or carbamazepine. The management of hyponatremia depends on the pathophysiologic mechanism and volume status. Hypovolemia requires use of parenteral saline. Correction of hyponatremia that has lasted more than 48 hours must be at a rate ≤ 8 mmol/L per day to avoid brain demyelination syndromes. Three percent (hypertonic) saline should only be used if there are seizures or a change in mental status from hyponatremia.

#### **Hypernatremia**

Hypernatremia could be the result of thirst impairment, inability to drink water, or the presence of central or nephrogenic diabetes insipidus. Central diabetes insipidus could be caused by leukemic infiltration of the pituitary gland or primary or metastatic tumors at that site. Nephrogenic diabetes insipidus could result from hypercalcemia, hypokalemia, or urinary tract obstruction. Treatment must restore extracellular volume by the use of hypotonic fluids, the amounts of which are calculated to decrease serum sodium levels by <10 mmol/L over the initial 24 hours.

#### **Hyperkalemia**

Although it is an important abnormality in patients with cancer, hyperkalemia may also be an artifact in such patients, for instance, from leukemic cell lysis. After ruling out this possibility, the next step is to identify excess potassium intake (oral or intravenous) or deficient excretion (chronic kidney failure, urinary tract obstruction, volume depletion, use of drugs causing hypoaldosteronism), or transcellular potassium shifts (eg, from TLS). For reference, the expected fractional excretion of potassium is 10% in



individuals with normal kidney function. Lower-than-expected values indicate impaired renal potassium excretion. Treatment for hyperkalemia in patients with cancer is the same as in any other patient.

### Hypokalemia

Hypokalemia can frequently occur as well. Excessive potassium losses could be gastrointestinal or renal. For instance, hypokalemia may be secondary to Fanconi syndrome due to multiple myeloma or drugs and thus associated with other electrolyte abnormalities such as hypophosphatemia. Hypokalemia with urinary potassium excretion  $> 20$  mmol/24 h or higher-than-expected fractional excretion is caused by kidney disorders. Abiraterone, used in metastatic castration-refractory prostate cancer, can cause hypokalemia related to excess mineralocorticoid concentration through adrenal CYP17 inhibition and reactive corticotropin secretion. Fluid retention and hypertension may occur. Paraneoplastic corticotropin secretion or adrenal cortical cancers are rare but challenging causes of hypokalemia.

Treatment of hypokalemia is urgent in the presence of weakness or arrhythmias. The intravenous route for potassium administration should then be used, but at a concentration  $\leq 40$  mEq/L and a rate  $\leq 10$  mEq/h if using a peripheral vein. In a less severe situation, it is better to replace the potassium deficit orally. Magnesium supplementation is needed when hypokalemia is caused by hypomagnesemia. Spironolactone or amiloride could be used for patients with hypokalemia caused by persistent cancer-related corticosteroid secretion. Hypokalemia due to abiraterone can be corrected by parallel use of prednisone.

### Hypomagnesemia

Hypomagnesemia is due to kidney or gastrointestinal losses. Kidney losses could be the result of chemotherapeutic agents, including cisplatin, carboplatin, oxaliplatin, ifosfamide, and epidermal growth factor receptor antibodies. For reference, fractional excretion of magnesium is  $\sim 4\%$  for a GFR in the normal range. If hypomagnesemia is not corrected, hypocalcemia and hypokalemia may ensue. Hypomagnesemia also could be induced by kidney wasting in the presence of hypercalcemia due to competition in the loop of Henle for paracellular reabsorption. The treatment is oral magnesium supplementation, but parenteral magnesium is required if there is arrhythmia or tetany.

### Hypermagnesemia

Hypermagnesemia could rarely occur. It is sometimes noted in patients with advanced kidney failure and high magnesium intake and is treated by stopping magnesium supplementation.

### Tumor Lysis Syndrome

TLS combines hyperkalemia, hyperphosphatemia, severe hyperuricemia, and secondary hypocalcemia. It has been reported in every cancer type but is primarily seen in tumors with a large burden or high proliferative rate, such as in hematologic malignancies. Its incidence varies from sporadic case reports in certain solid tumors to  $>25\%$  in high-grade B-cell acute lymphoblastic leukemia. TLS is due to rapid release into the extracellular space of substances from lysing malignant cells, with the rapid serum increase in phosphate, potassium, and uric acid levels, the latter derived from the breakdown of nucleic acids. This can lead to severe oliguric AKI due to tubular obstruction with uric acid crystals possibly associated with intrarenal deposition of calcium phosphate. Kidney failure then limits potassium, phosphate, and uric acid clearance, aggravating these abnormalities and leading to secondary hypocalcemia due to calcium-phosphate deposits in tissues. Prevention of TLS may be more effective than treatment. One must identify those at high risk in whom preventative measures must be applied.

TLS should be considered in any patient with AKI and a significant burden of malignant disease, particularly in the setting of hyperuricemia, hyperkalemia, and hyperphosphatemia. Accurate risk assessment is vital to prevent TLS. Patients at risk of TLS should receive at least 3 L/d of oral or intravenous fluid before initiation of chemotherapy, provided they have no contraindications to volume expansion, to induce high urine output. Among patients at medium or high risk of developing TLS, a prophylactic xanthine oxidase inhibitor such as allopurinol (or febuxostat in cases of allopurinol hypersensitivity or reduced kidney function) should be started. In patients with high-risk tumor types, consensus guidelines suggest the prophylactic use of recombinant urate oxidase (rasburicase) before chemotherapy. Using intravenous bicarbonate perfusion to avoid uric acid precipitation by inducing extracellular alkalization is no longer advised because of the high risk for calcium phosphate deposition in tissues and secondary severe symptomatic hypocalcemia.

Hemodialysis, continuous or intermittent, may be needed for AKI caused by TLS, as in any case of AKI.

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## ACUTE KIDNEY INJURY

### Epidemiology

AKI is a common condition that is associated with increases in costs, length of hospital stay, morbidity, and mortality. A Danish population-based study reported the incidence of AKI (defined as doubling of serum creatinine) to be 18% in the first year after cancer diagnosis. This is very much higher than the incidence of AKI in the general population, which is about 1 per 1,000 per year. Patients at higher risk for developing AKI include those with kidney cancer, multiple myeloma, liver cancer, and acute leukemia and lymphoma undergoing induction chemotherapy. Patients undergoing hematopoietic stem cell (HSC) transplantation or nephrectomy for renal cell cancer and those admitted to the intensive care unit (ICU) are also at higher risk. In addition, diabetes, chemotherapy, intravenous contrast, hyponatremia, and antibiotics are associated with increased risk of AKI. A recent study from the MD Anderson Cancer Center reported that 12% of hospitalized patients developed AKI, a quarter of whom required dialysis. In this series, more than half the patients developed AKI more than 2 days after hospitalization. This points to a window of opportunity for preventive or mitigating interventions to optimize the renal status of the patient before chemotherapy, perhaps by hydration and removal of nephrotoxic medications.

### Causes and Treatment of AKI

The causes of AKI can be divided into cancer-specific and cancer-nonspecific causes. Cancer-specific causes include nephrotoxic chemotherapy, cast nephropathy, obstructive nephropathy, hypercalcemia, lymphomatous infiltration of the kidney, hepatic sinusoidal obstruction syndrome, thrombotic microangiopathy, and TLS. Cancer-nonspecific causes are volume depletion, medication (diuretics, angiotensin-converting enzyme [ACE] inhibitors, and nonsteroidal anti-inflammatory drugs), and contrast nephropathy. The workup and treatment are similar to those for AKI in the general population and focus on establishing the prerenal, renal, or postrenal nature of AKI (Table 2); optimizing volume status; treating the underlying cause; and, if necessary, renal replacement

therapy. As in the general population, the dominant causes of AKI in critically ill patients with cancer are sepsis and hypotension (Fig 1). Thus, improving the diagnosis and treatment of AKI in the general population will also benefit patients with cancer and AKI.

### Role of Kidney Biopsy

In a recent report, only 0.66% of kidney biopsies performed at Brigham and Women's Hospital in Boston were done in patients with cancer. Nephrologists appear reluctant to perform a kidney biopsy in patients with cancer, but tubulointerstitial nephritis is an under-recognized yet treatable entity in patients with cancer that may only be apparent on biopsy. Ifosfamide, BCG, tyrosine kinase inhibitors, premetrexed, and anti-CTLA4 antibodies have been associated with tubulointerstitial nephritis in patients receiving chemotherapy. Glucocorticosteroids may be effective in treating the condition.

### Treatment by Dialysis

The available data suggest that hemodialysis should be offered to patients in the ICU with both cancer and AKI. Kidney recovery is possible and survival of select patients with cancer is similar to that of noncancer ICU patients with AKI requiring hemodialysis. In patients with cancer and AKI, sustained low efficiency dialysis may be the treatment of choice in the ICU.

### Consequences of AKI

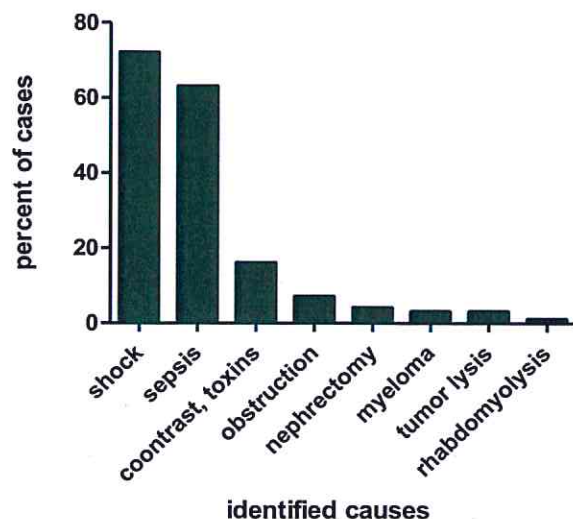
AKI can result both in under- and overtreatment; the former due to delay or cancellation of chemotherapy

Table 2. Types of Acute Kidney Injury

Site of Injury	Cause
Prerenal	Hypovolemia, cardiac failure, hepatorenal syndrome
Renal	
Glomeruli	Small-vessel disease: TMA, vasculitis, atheroembolism, light chain-associated glomerular disease
Vasculature	
Vein	Renal vein thrombosis
Artery	Arterial occlusion, large-/medium-vessel vasculitis
Interstitial	Drugs, infections, systemic diseases
Tubules	
Acute tubular necrosis	Ischemia, nephrotoxins, rhabdomyolysis, radiocontrast
Intratubular obstruction	Cast, crystalluria, tumor lysis syndrome, drugs
Postrenal	Tumoral invasion of ureter, retroperitoneal fibrosis, bladder outlet obstruction, renal calculi, papillary necrosis

Abbreviation: TMA, thrombotic microangiopathy.





**Figure 1.** Causes of acute kidney injury in critically ill cancer patients. Data from Soares et al (Prognosis of critically ill patients with cancer and acute renal dysfunction. *J Clin Oncol*. 2006;24:4003-4010).

and the latter due to unadjusted dosing of chemotherapy. A recent study showed that the occurrence of AKI was associated with a decreased rate of cancer remission. AKI after HSC transplantation is associated with later development of CKD, but whether this is true for patients with cancer in general is not known. Because survival is improving in patients with cancer, the development of CKD after AKI could have a major impact on morbidity and mortality. Automated detection of the occurrence of AKI, early involvement of a nephrologist, and better preventive, mitigating, and treatment strategies may improve the outcome of AKI in patients with cancer.

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#### CANCER CHEMOTHERAPY NEPHROTOXICITY

Obvious renal toxicity may result from hemodynamic changes, parenchymal injury, and/or urinary obstruction. More subtle kidney damage (eg, acid-base abnormalities, disorders of water balance disorders, electrolyte imbalances, mild urinary sediment abnormalities, and tubulopathy) are frequently unrecognized and therefore the true incidence of nephrotoxicity is difficult to determine. Most episodes of medication-induced GFR loss are reversible, with kidney function returning to baseline when the drug is withdrawn. CKD can occur by glomerular scarring or tubulointerstitial inflammation. This review is limited to frequently used agents such as platinum, methotrexate, and gemcitabine and to more recent molecules such as tyrosine kinase inhibitors. Other anticancer drug-induced nephrotoxicities are summarized in Table 3.

The most frequent nephrotoxic drug reaction is AKI, characterized by a rapidly increasing serum creatinine level. Each drug has its own pattern of injury. If glomerular injury predominates, proteinuria may be in the nephrotic range or at lower levels in association with microscopic hematuria. Hypertension predominates in vascular or glomerular syndromes. Signs of allergic reaction are absent in most patients.

#### Platinum Salts

Cisplatin and its analogues carboplatin and oxaliplatin are widely used. Early trials with cisplatin reported that >70% of patients developed dose-related AKI. At high cisplatin doses, 42% of treated patients had nephrotoxic injury. In a meta-analysis of randomized phase 2 and 3 clinical trials comparing first-line platinum-based chemotherapy to the same regimen without platinum, platinum was associated with a significant increase in nephrotoxicity (18 trials; 4,384 patients; odds ratio, 3.09; 95% confidence interval, 1.88-5.06;  $P < 0.0001$ ). Carboplatin is considered to be less nephrotoxic than cisplatin. Only rare cases of acute tubular necrosis induced by oxaliplatin have been reported. Clinical practice guidelines have been published on the prevention of cisplatin-induced kidney injury. They include correction of preexisting volume depletion, appropriate provision of parenteral saline during drug administration and the following days, and prevention of chemotherapy-induced nausea and vomiting.

Cisplatin has also been associated with hemolytic uremic syndrome (HUS), either alone or in combination



Table 3. Nephrotoxicity Related to Some Anticancer Drugs

Drug	Nephrotoxicity profile	Prevention or Management
Azacitidine	Fanconi syndrome, nephrogenic diabetes insipidus	Discontinuation of the drug
Carmustine	Decreased kidney perfusion induced by hypotension (resolves a few hours after completion of carmustine administration)	Administration of supplemental crystalloid fluid; reduction of the carmustine infusion rate by 50% or drug discontinuation
	CKD 1 to 24 mo following completion of therapy	Vasopressor administration; antihypertensive medication should be discontinued 24 h preceding and withheld on the day of carmustine administration
Cyclophosphamide	SIADH, nephrogenic diabetes insipidus	Discontinuation of the drug
	Hemorrhagic cystitis	Aggressive hydration and mesna use
Ifosfamide	Fanconi syndrome, CKD, SIADH, nephrogenic diabetes insipidus; risk factors include cumulative ifosfamide dose > 50 g/m <sup>2</sup> , preexisting GFR loss and/or nephrectomy, age ≤ 12 y, Wilms tumor, previous cisplatin treatment	If possible, ifosfamide should be discontinued in patients developing signs of moderate to severe AKI during therapy; oral and/or IV fluid and electrolyte supportive therapy should be provided
Interferon	Acute tubular necrosis and variable glomerular lesions, proteinuria in up to 5%-20% of patients; normalization of Scr level generally occurs within weeks to months of drug discontinuation; SIADH	If possible, treatment with interferon alfa should be discontinued with the onset of AKI
	TMA	Prompt diagnosis, early discontinuation of the drug, and supportive treatment may improve the outcome
IL-2	Decreased kidney perfusion induced by capillary leak syndrome; time and dose dependent; occurs 24-48 h after initiating therapy; risk factors include baseline CKD, previous hypertension, male sex, sepsis, cardiac dysfunction	Supplemental crystalloid fluid administration; diuresis; discontinuation of antihypertensive therapy prior and during IL-2 infusion
Mercaptopurine	Fanconi syndrome	Discontinuation of the drug
Mitomycin C	TMA; risk at a cumulative dose > 30 mg/m <sup>2</sup> ; generally arises 4-8 wk after the end of therapy but the onset may occur immediately after treatment or up to 9 mo later; recovery is possible but CKD is usually progressive and dialysis is required in almost 1/3 of patients; case fatality rate is >50% and median time to death is ~4 wk	Prompt diagnosis, early discontinuation of the drug, and supportive treatment may improve the outcome
Streptozotocin	Fanconi syndrome, CKD, glomerular toxicity, and kidney failure	Discontinuation of the drug (continued treatment generally results in irreversible injury)

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; IL-2, interleukin 2; IV, intravenous; Scr, serum creatinine; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; TMA, thrombotic microangiopathy.

with bleomycin and vinblastine. Signs of HUS occur 1 to 4 months after the last dose of cisplatin. Interventions with aspirin, dipyridamole, fresh frozen plasma, plasma exchange, and red blood cell transfusions have shown variable efficacies.

A significant issue with carboplatin is the calculation of its dosage using the Calvert formula: total dose of carboplatin (mg) = (AUC) × (GFR + 25), where AUC (area under the curve) is the serum concentration being targeted for the drug. The Calvert formula was established using measured GFR using radiolabeled chromium-EDTA as a filtration marker. However, in clinical practice, creatinine clearance (calculated by the Cockcroft-Gault formula) or eGFR (calculated by the MDRD Study or CKD-EPI equation) are routinely

used. There are only sparse data evaluating the accuracy of the Calvert formula with these estimates.

### Methotrexate

An article in the 1970s reported AKI in 30% to 50% of patients after high-dose methotrexate therapy with leucovorin rescue. In the same era, a single-center study of 64 patients recorded 3 deaths secondary to AKI, and an analysis of 498 patients treated according to National Cancer Institute protocols found that 29 died after high-dose methotrexate therapy, establishing a mortality rate of 6%. However, in a report published in 2004, only 1.8% of patients with osteosarcoma who were treated with high-dose methotrexate developed significant nephrotoxicity.



Methotrexate is renally excreted both intact and as 7-hydroxymethotrexate, a more insoluble metabolite. In acid urine (pH < 5.5), both compounds precipitate, whereas solubility is 10-fold greater at neutral pH. Furthermore, a dramatic increase in methotrexate-creatinine clearance ratio is observed when urinary pH is increased from 5.5 to 8.4.

The variable incidence of high-dose methotrexate-induced AKI may be genetically determined. Anionic drugs such as methotrexate can be eliminated by multidrug resistance protein 2 (MRP2) transporter, which is expressed at the luminal side of renal proximal tubular cells. A heterozygous mutation of MRP2 is associated with reduced methotrexate excretion and increased nephrotoxicity; as a result, candidates for methotrexate therapy might benefit from MRP2 functional testing.

High-dose methotrexate-induced nephrotoxicity is managed with parenteral crystalloid and alkalization (to provide adequate urine output), high-dose leucovorin, dialysis-based methods of methotrexate removal, and thymidine. For patients with delayed methotrexate excretion and high plasma concentrations, use of the recombinant enzyme carboxypeptidase-G<sub>2</sub> (CPDG<sub>2</sub>) cleaves methotrexate to inactive metabolites, potentially lowering plasma methotrexate concentrations.

### Gemcitabine

Gemcitabine has been associated with thrombotic microangiopathy (TMA), which is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and various ischemic end-organ injuries, and has been reported with gemcitabine. In terms of pathology, TMA is marked by endothelial cell swelling, vessel wall thickening, intraluminal platelet thrombi, and microvascular occlusion. TMA may present as HUS or in some cases has predominant involvement of the central nervous system, presenting as thrombotic thrombocytopenic purpura, demonstrating. Based on adverse-event reporting through 1997, the manufacturer of gemcitabine estimated the incidence of TMA with gemcitabine use as 0.015% (reports range from 0.02%-0.3%). Although under-reporting is possible, TMA with gemcitabine remains rare in comparison to incidence rates of 2.6% to 13.0% for either malignancy-induced or chemotherapy-induced HUS. Signs and symptoms of TMA usually develop within 1 to 2 months of the last gemcitabine dose and the outcome with TMA is poor: mortality rates range from 10% to 70%.

Although effective strategies for preventing or reducing the severity of gemcitabine-associated TMA have not been identified, several have been tested: exchange transfusion, hemodialysis, fresh frozen plasma transfusion, immunoadsorption, plasmapheresis,

immunosuppressive therapies (azathioprine, corticosteroids, or vincristine), and antiplatelet/anticoagulant therapies (antiplatelet drugs, heparin, prostacyclin, or splenectomy). If the drug is still being given when gemcitabine-associated TMA is identified, it must be discontinued. Kidney function could recover completely, but delayed diagnosis is associated with CKD, progression to end-stage renal disease, and death due to progressive disease.

### Tyrosine Kinase Inhibitors

Among tyrosine kinase inhibitors, the pattern of kidney injury is glomerular for those targeted to vascular endothelial growth factor (VEGF) receptors. These drugs (sunitinib, sorafenib, axitinib, and cediranib) are used to treat kidney cancer because of its high VEGF expression, whether sporadic or from the *VHL* gene mutation. VEGF is important in maintaining glomerular podocyte and endothelial function. Its blockade leads to proteinuria in more than half the patients treated; in <10% of cases, to nephrotic syndrome. Rarer still is TMA caused by endothelial injury, which is an indication to stop treatment. Hypertension occurs in ≥30% of treated patients and might be a marker of drug efficacy, but is not an indication to stop VEGF antagonists. Similar toxicities are described for antiangiogenic antibodies, including bevacizumab and ramucirumab.

Other tyrosine kinase inhibitors such as crizotinib and vemurafenib, which act on ALK and BRAF, were not associated with kidney injury in development trials. However, kidney effects have occurred in practice, with cases of AKI, sometimes severe, rapidly reported in the literature. Tyrosine kinase inhibitors also may cause interstitial nephritis. The BCR-ABL inhibitor imatinib causes phosphaturia, as mentioned in the fluid and electrolyte section of this article.

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## PARANEOPLASTIC GLOMERULAR DISEASES

Paraneoplastic glomerular diseases are manifestations caused by products secreted by cancer cells, such as tumor antigens, hormones, growth factors, or cytokines. Unexplained proteinuria can be an indication to a search for malignancy, especially in older patients.

### Epidemiology

Table 4 shows the glomerular lesions linked to cancer. The most common lesion in solid cancers is

membranous nephropathy (MN). In patients with MN, the prevalence of solid tumors ranges from 1% to 22%; for instance, a prevalence of 10% was found in a large retrospective study of 240 individuals with biopsy-proven MN. At the time of biopsy, only 50% of patients may have symptoms related to their cancer. Malignancy is diagnosed in most within a year of detection of MN; however, the risk of finding cancer could persist for more than 10 years from the time of the biopsy. In one report of 21 cases of minimal change disease and Hodgkin lymphoma, nephrotic syndrome appeared in 38%, 19%, and 43% of patients before, with, and after the cancer diagnosis, respectively. In one report of glomerulonephritis and chronic lymphocytic leukemia, B-cell proliferation and glomerulopathy were simultaneously diagnosed in 7 of 13 (5%) patients.

### Diagnosis

Box 1 shows features that may point to paraneoplastic MN. Confirmation of paraneoplastic glomerular diseases is based on remission of the symptoms and histologic lesions after cure or remission of the cancer, relapse of kidney disease if the cancer recurs, and existence of a pathophysiologic link between cancer and the glomerulopathy (eg, cancer antigen trapped in the glomerular filtration barrier).

Glomerular disease, notably nephrotic syndrome related to MN, could also be noted in patients following HSC transplantation. In the case of minimal change disease detection, it seems prudent to look for recurrence of the primary hematologic malignancy.

There is a temporal relationship between cessation of immunosuppressive drugs and nephrotic syndrome, concomitantly with the development of graft-versus-host disease, especially after allogeneic HSC transplantation.

Table 4. Classification of Paraneoplastic Glomerulopathies

Rank	Solid Cancer	Hematologic Cancer
1	Membranous nephropathy (lung, gastrointestinal, kidney cancer)	Minimal change disease (Hodgkin lymphoma, thymoma)
2	Minimal change disease (lung, kidney, colorectal cancer)	Membranoproliferative glomerulonephritis (chronic lymphocytic leukemia, non-Hodgkin lymphoma)
3	Crescentic glomerulonephritis (kidney, gastric cancer)	Membranous nephropathy (chronic lymphocytic leukemia, non-Hodgkin lymphoma)
4	Membranoproliferative glomerulonephritis (lung cancer, melanoma, kidney cancer)	Crescentic glomerulonephritis (chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphoma)
5	IgA nephropathy (kidney cancer)	IgA nephropathy (non-Hodgkin lymphoma)
6	Focal segmental glomerulosclerosis (kidney cancer)	Focal segmental glomerulosclerosis (Hodgkin lymphoma)
7	AA amyloidosis (kidney cancer)	AA amyloidosis (Hodgkin and non-Hodgkin lymphoma)

Note: Ranking of most to least frequent glomerulopathies associated with solid (first column) and hematologic (second column) cancers. For each glomerulopathy, the specific cancers that are most commonly associated are given in parentheses.

Abbreviation: IgA, immunoglobulin A.

Adapted from Bacchetta J et al (Paraneoplastic glomerular diseases and malignancies. *Crit Rev Oncol Hematol*. 2009;70:39-58) and Jhaveri et al (Glomerular diseases seen with cancer and chemotherapy: a narrative review. *Kidney Int*. 2013;84:34-44).



**Box 1. Characteristics Suggestive of Paraneoplastic Membranous Nephropathy**

- Age > 65 y
- Smoking history > 20 pack-y
- Absence of PLA<sub>2</sub>R1 antibodies
- Presence of high IgG1 and IgG2 subtype deposits and >8 inflammatory cells per glomerulus observed in kidney biopsy specimen
- Regression of glomerular lesions and proteinuria upon remission of the cancer
- No obvious other cause

Abbreviations: IgG, immunoglobulin G; PLA<sub>2</sub>R1, antiphospholipase A<sub>2</sub> receptor.

**Treatment of Paraneoplastic Glomerular Diseases**

Cure or remission of the cancer is the primary goal. It is not known whether treatments such as cyclophosphamide or rituximab for MN will be effective for its paraneoplastic variant. It is prudent to also use nephroprotective therapies, including a low-salt diet and appropriate antihypertensive therapy, to try to slow progression to end-stage renal disease.

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**PARAPROTEIN-RELATED KIDNEY DISEASE**

Paraproteins are directly nephrotoxic and a wide and diverse range of kidney diseases is associated with them (Fig 2). Multiple myeloma, which has a yearly incidence of about 60 per million general population, is the most common cause of paraprotein-

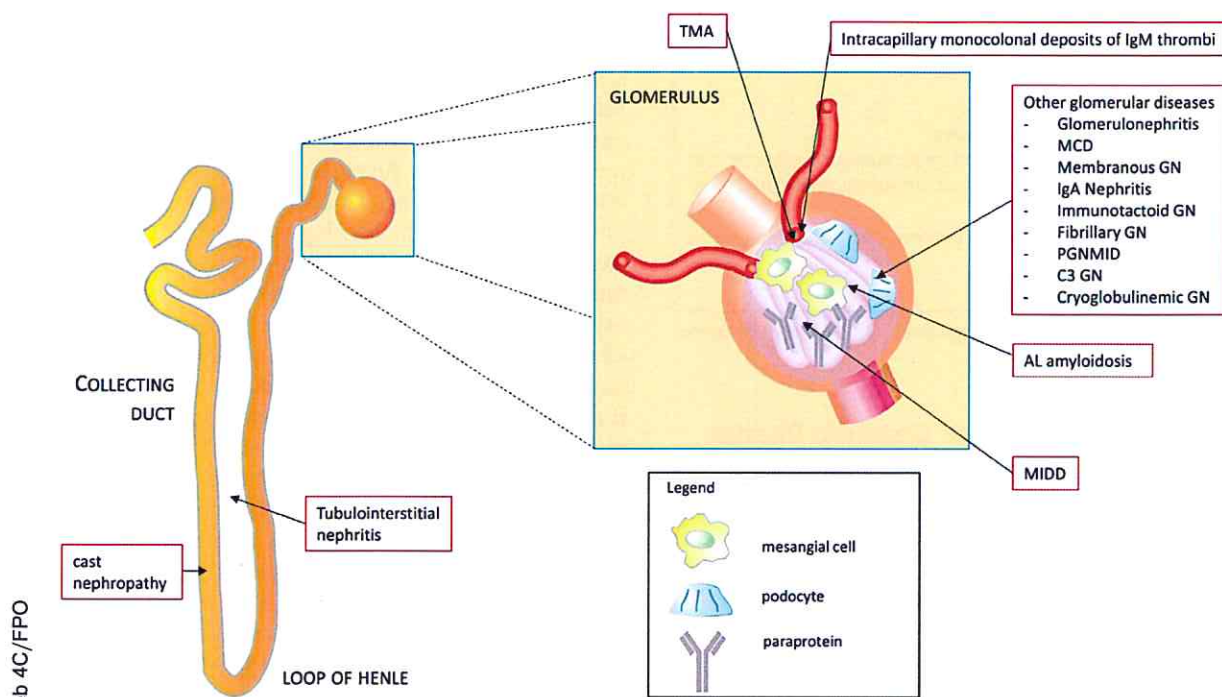
induced kidney disease. At the time of diagnosis, half the patients with multiple myeloma will have reduced kidney function and 10% will require dialysis. CKD stage 5 is a poor prognostic factor in this setting, and its appearance is a medical emergency because recovery of kidney function is unlikely in patients with multiple myeloma unless therapy is initiated promptly. Although autologous stem cell transplantation remains the treatment of choice, there are only limited data available in patients with multiple myeloma with kidney disease. With the introduction of novel chemotherapeutics such as bortezomib, kidney outcomes of patients with multiple myeloma have improved significantly. Data regarding plasmapheresis in treating cast nephropathy are limited and do not allow for strong recommendation of this treatment. Recently, dialysis using membranes with a high-molecular-weight cutoff has been advocated for treating cast nephropathy, but there are no definite data on this question.

Diagnosis of kidney diseases associated with plasma cell malignancies has improved with the advent of the serum free light chain assay and laser microdissection-mass spectrometry. The free light chain assay, in combination with serum protein electrophoresis and immunofixation electrophoresis, is advocated for screening and monitoring of monoclonal gammopathies; normal  $\kappa:\lambda$  ratios are 0.37 to 3.1 and 0.26 to 1.65 in patients with and without CKD, respectively. With laser microdissection-mass spectrometry, selective isolation of amyloid material from kidney biopsy and subsequent protein analysis using mass spectrometry allows for more precise diagnosis of paraprotein kidney diseases. The most common kidney diseases associated with plasma cell dyscrasia are multiple myeloma and AL amyloidosis. However, several other glomerular diseases have been reported to be paraprotein related, and the number is growing: light and heavy chain deposition disease, immunotactoid glomerulonephritis, fibrillary glomerulonephritis, and proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Monoclonal gammopathy of undetermined significance is present in 2% to 4% of people 50 years or older and has an annual rate of progression to multiple myeloma of 0.5% to 1.5%. Recently, the term monoclonal gammopathy with renal significance was proposed to distinguish monoclonal gammopathies resulting in the development of kidney diseases in patients with B-cell clones who do not meet the definition of multiple myeloma or lymphoma.

**Treatment**

The optimal treatment of multiple myeloma and paraprotein-related kidney disease is evolving rapidly with the availability of novel and more targeted





**Figure 2.** Paraprotein-related kidney injury. A growing number of kidney diseases have been associated with paraproteinemia. Abbreviations: GN, glomerulonephritis; Ig, immunoglobulin; MCD, minimal change disease; MIDD, monoclonal immunoglobulin deposition disease; PGNMID, proliferative glomerulonephritis with monoclonal immune deposits; TMA, thrombotic microangiopathy.

treatments. However, high-dose chemotherapy in combination with stem cell transplantation remains the standard of care for eligible patients. Hematologists will guide the treatment but nephrologists will often be consulted because many patients with myeloma may have reduced kidney function at some point during their illness.

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#### URINARY TRACT OBSTRUCTION

##### Occurrence and Prognosis

Urinary tract obstruction is an ominous development in adults with cancer. It can occur as a presenting feature, in instances of prostate or bladder cancer or of nonurologic cancers such as lymphomas or gynecologic cancers. The median survival of these patients is about 100 days. Survival can be further predicted by assessment of metastatic events, degree of hydronephrosis, and serum albumin level. Thus, 3 or more metastases, lesser degrees of hydronephrosis, and serum albumin level < 3 mg/dL predict 6-month survival of 2%, whereas none of these risk factors predicts 70% survival over the same period. This assessment is important in deciding on interventions to relieve obstruction.

In children with urinary tract obstruction caused by cancer, survival is much higher: 80% live 5 years postpresentation. Survival rate differences between adults and children could relate to the better ability to



treat cancers that cause the condition in children (eg, neuroblastoma).

### Diagnosis

Kidney ultrasound or computed tomography will identify most cases of urinary tract obstruction. A few patients will develop kidney failure due to obstruction with little or no dilation of the urinary tract, which can be due to encasement of the ureters by metastatic cancer in the retroperitoneum. Unilateral or bilateral obstruction may cause pain and predispose to infection. Bilateral obstruction will cause collecting duct malfunction, resulting in the inability to concentrate urine and variable polyuria. It also will impair potassium excretion, leading to hyperkalemia.

### Treatment and Prognosis

Retrograde or antegrade stenting have been used to relieve pain and improve kidney function. It is possible that percutaneous nephrostomy tubes and antegrade ureteric stenting have a better outcome as compared with retrograde approaches. Tube dislodgement and infection may complicate both. In 2 recent case series, patients treated with percutaneous nephrostomy and/or ureteric stents reportedly spent 25% to 30% of their remaining lifetime in the hospital. A palliative care consultation should be sought when an adult patient with cancer develops urinary tract obstruction.

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## CANCER IN CKD, DIALYSIS, AND TRANSPLANT PATIENTS

### General

#### Epidemiology and Screening

Population studies show a significant excess of cancer in people with end-stage renal disease and

earlier stages of CKD. In patients with CKD who are not dependent on renal replacement therapy, there is significant risk for lip, Kaposi, thyroid, and especially kidney and urinary tract cancer. The pattern is similar for patients treated with long-term dialysis. In kidney transplant recipients, skin cancer and lymphoma become the dominant cancers; in addition, the standardized incidence ratio is well above the expected value for kidney and urinary tract cancers. This raises the question of surveillance and screening to make earlier diagnoses of these cancers and improve treatment outcomes. However, most cancer treatment trials exclude the CKD population. Thus, the treatment benefit that is achieved by screening and early diagnosis is unknown for people with CKD who develop cancer. In an analysis using known dialysis mortality rates and that assumed equivalent results of treatment, the benefit of screening dialysis patients for usual cancers like breast, prostate, and colon was found to be insignificant. This lack of benefit occurs because the major causes of death in these patients are cardiovascular and infectious in nature, so death from cancer is less meaningful as a clinical concern. However, cancer is a feared complication of kidney transplantation. Farrugia et al reported significant cancer-related mortality in people with functioning kidney transplants and advised heightened surveillance. However, screening for common cancers such as breast, prostate, and colon is not beneficial in kidney transplant recipients.

### Diagnosis and Treatment

Delayed diagnosis of cancer in people with CKD can occur (eg, pulmonary congestion might obscure a thoracic cancer). However, except for prostate cancer, the stage of cancer at the time of diagnosis is not different in dialysis patients compared to the general population. There are no data for this question for patients with non-dialysis-dependent CKD or people with functioning kidney transplants.

Treating cancer in people with CKD may be less effective and lead to higher mortality rates than when treating age-matched people without CKD. This may reflect altered characteristics of cancer in patients with CKD or may occur because treatment is more difficult to administer on schedule at effective doses. Morbidity and mortality from surgery or chemotherapy are likely to be higher in people with versus without CKD. There are highly effective chemotherapy drugs such as cisplatin that either are not used at all or are very cumbersome to administer to patients with CKD. There are no evidence-based standards for cancer treatment for patients with non-dialysis-dependent CKD, patients receiving dialysis, or those with a functioning kidney transplant. The nephrotoxicities and dose adjustments of



cancer chemotherapy in patients with CKD are discussed in the “Cancer Chemotherapy Nephrotoxicity” section of this article.

## **Kidney-Specific Cancer**

### **Acquired Cysts and Cancer**

Cyst formation in noncystic failing kidneys may be complicated by cancer. At a rate about 4 times that of the general population, kidney cancers occur in people with dialysis- or non-dialysis-dependent CKD and in individuals with functioning kidney transplants. These cancers can be papillary or clear cell type and can be asymptomatic, identified radiologically, or present with pain or hematuria. Screening is probably not beneficial or cost-effective. There is no evidence-based guideline on whether uni- or binephrectomy is preferable. Because CKD and its duration correlate with cyst formation and CKD progression can be markedly slowed with newer treatments, it is likely that acquired cysts and their associated cancers will increase in prevalence in the foreseeable future.

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## **KIDNEY CANCER**

### **Overview**

Kidney cancer is no longer just an issue for urologists. This has become clear as experience with acquired cysts and their associated cancers has grown.

Kidney cancer is more common in people with CKD, and surgery for kidney cancer may result in AKI, CKD, progression of preexisting CKD, or development of end-stage renal disease.

### **Diagnosis**

Diagnosis of kidney cancer in patients with CKD is based on symptoms, though incidental diagnosis by imaging is increasing. Urinary and serum markers may help in diagnosis: urinary kidney injury marker 1 (KIM-1) appears promising but is not in general use. Computed tomography remains the standard for diagnosis and preoperative staging. New magnetic resonance imaging techniques may enable preoperative histologic diagnosis. Kidney biopsy of small kidney masses appears to be safe and may show benign lesions, which avoids the need for surgery.

### **CKD After Kidney Cancer**

CKD after nephrectomy is associated with increased mortality, especially due to cardiovascular causes. Patients who have a preoperative serum creatinine level  $\geq 2$  mg/dL appear at increased risk of these adverse outcomes. Many studies report that radical nephrectomy is associated with lower patient survival when compared to partial nephrectomy, although a prospective trial comparing partial to radical nephrectomy could not confirm this effect.

Size matters when managing kidney masses. For lesions  $< 3.5$  cm, surveillance may be preferable to surgery. For cancers up to 7 cm in diameter, partial nephrectomy is safe and may cause less subsequent kidney disease than radical nephrectomy. Some larger cancers may be suitably treated by partial rather than radical nephrectomy. Surgical improvements, including reduced clamp time and laparoscopic and robotic techniques, appear to reduce acute and chronic complications. Nonetheless, cancers  $> 7$  cm in diameter have a higher risk of cancer-related morbidity and mortality. Fear of worsening kidney function should not force the surgeon to do a partial nephrectomy when it is more appropriate to remove the entire kidney.

When CKD occurs after surgery for kidney cancer, management is the same as that for any cause of CKD. A patient who has only a fraction of normal kidney tissue remaining after cancer surgery faces a physiologic situation in some ways similar to that of the rat remnant kidney model of progressive loss of kidney function. In this model, a low-protein diet and/or ACE inhibition may slow the loss of kidney function. Perhaps this explains why patients with remnant kidneys may survive long term and do not necessarily experience progressive kidney disease leading to the need for dialysis therapy. The principles of care for these patients should be the same as for



any cause of CKD: control of blood pressure, use of ACE inhibitors, and relief of metabolic acidosis. Reliable markers of cancer recurrence need to be developed.

Treating metastatic kidney cancer now includes agents that are truly effective and prolong life yet have definite toxicities to the kidney and other organs (see Cancer Chemotherapy Nephrotoxicity section).

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### RADIATION NEPHROPATHY

#### Epidemiology

Radiation nephropathy is uncommon. Its classic occurrence is after radiotherapy for testicular cancer in which treatments are given over a month or longer in total doses  $> 20$  Gy. It occurs in adults or children undergoing HSC transplantation that is preceded by chemo-irradiation conditioning. It also occurs after radionuclide therapies that deliver radioisotope to kidneys in sufficient doses. However, the doses of

diagnostic x-ray, computed tomography, or radionuclide are well below those that cause kidney injury.

#### Presentation and Management

Radiation nephropathy occurs after the radiotherapy is complete, with a latent period of several months or more. Proteinuria, azotemia, and hypertension are the presenting features. Histologic features include mesangiolysis and tubulointerstitial scarring, with only scant inflammation. Unilateral kidney irradiation may cause renin-dependent hypertension with secondary injury to the nonirradiated kidney. Management is as for any form of CKD. As is seen in experimental models of radiation nephropathy, ACE inhibitors or angiotensin receptor blockers may be particularly effective therapies.

Newer radiotherapy protocols, for instance for pancreatic or gastric cancer, may irradiate sufficient kidney volumes at high enough doses to cause kidney injury. Coordination with radiation oncology teams is important in establishing the diagnosis in such cases.

#### Additional Readings

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### KIDNEY DISEASE AFTER HSC TRANSPLANTATION

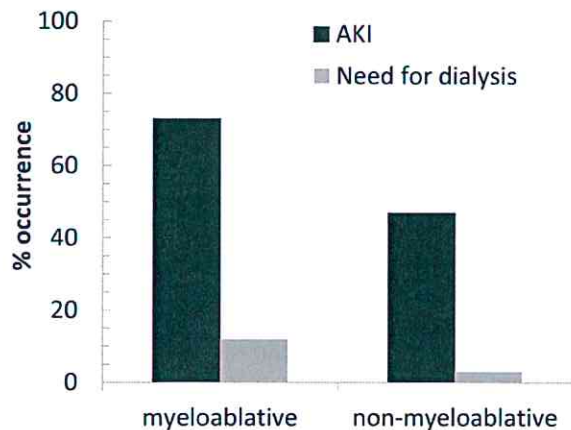
#### Acute Kidney Injury

AKI often complicates HSC transplantation and is more common after myeloablative versus non-myeloablative HSC transplantation (Fig 3). This might be expected because lower doses of chemotherapy and radiotherapy are used for non-myeloablative HSC transplantation. The median time to AKI occurrence is 20 to 30 days after the procedure. Sepsis and use of nephrotoxic antibiotics or calcineurin inhibitors are common causes of AKI, but other causes (such as TLS) are possible. AKI after HSC transplantation is associated with a  $>50\%$  increase in mortality post-HSC transplantation and is strongly associated with the development of CKD.

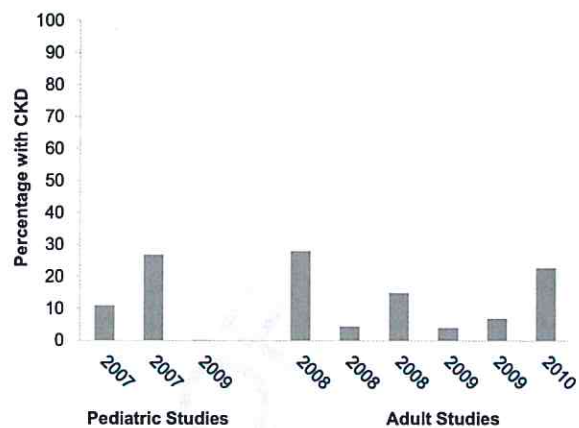
#### Diagnosis and Management

Diagnosis of AKI after HSC transplantation may be compromised by lesser elevations in serum creatinine level than expected because of previous cancer and loss of muscle mass. If dialysis is needed, it is not known whether continuous or intermittent dialysis is preferentially effective.





**Figure 3.** The occurrence of acute kidney injury (AKI) after hematopoietic stem cell (HSC) transplantation. AKI is more common after myeloablative HSC transplantation and more often leads to a requirement for dialysis. AKI is defined here as more than doubling of serum creatinine level. Data from Parikh et al (Comparison of ARF after myeloablative and nonmyeloablative hematopoietic cell transplantation. *Am J Kidney Dis.* 2005;45:502-509).



**Figure 4.** The prevalence of chronic kidney disease (CKD) after hematopoietic stem cell transplantation in children and adults, based on studies from 2007 onward. The arithmetic average for all studies is 13%. Reproduced from Cohen et al (Chronic kidney disease after hematopoietic stem cell transplantation. *Semin Nephrol.* 2010;30:627-634) with permission from Elsevier.

### Chronic Kidney Disease

As stated, AKI after HSC transplantation is associated with the development of CKD. This may occur as it can after any AKI event, related to residual kidney injury and scarring. Other specific causes of CKD after HSC transplantation are well known and include drug toxicities (such as from calcineurin inhibitors), radiation nephropathy, and MN (Fig 4).

#### Diagnosis and Management

CKD that presents with features of TMA within a year after HSC transplantation is likely due to calcineurin toxicity or radiation nephropathy. CKD with nephrotic-range proteinuria in a patient with chronic graft-versus-host disease may indicate minimal change disease or MN. A history of ifosfamide and cisplatin use in a patient with phosphaturia points to these chemotherapies as culprits. Managing CKD in a patient who received an HSC transplant is complicated by comorbid conditions such as cardiotoxicity from previous chemotherapy; however, stabilization of kidney function can be achieved. Unfortunately, end-stage renal disease is much more common after HSC transplantation than in age-matched healthy individuals. Mortality of maintenance dialysis patients is high. Kidney transplantation is a well-described option and can be done without immunosuppression if the kidney donor is the same person who donated the HSCs.

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